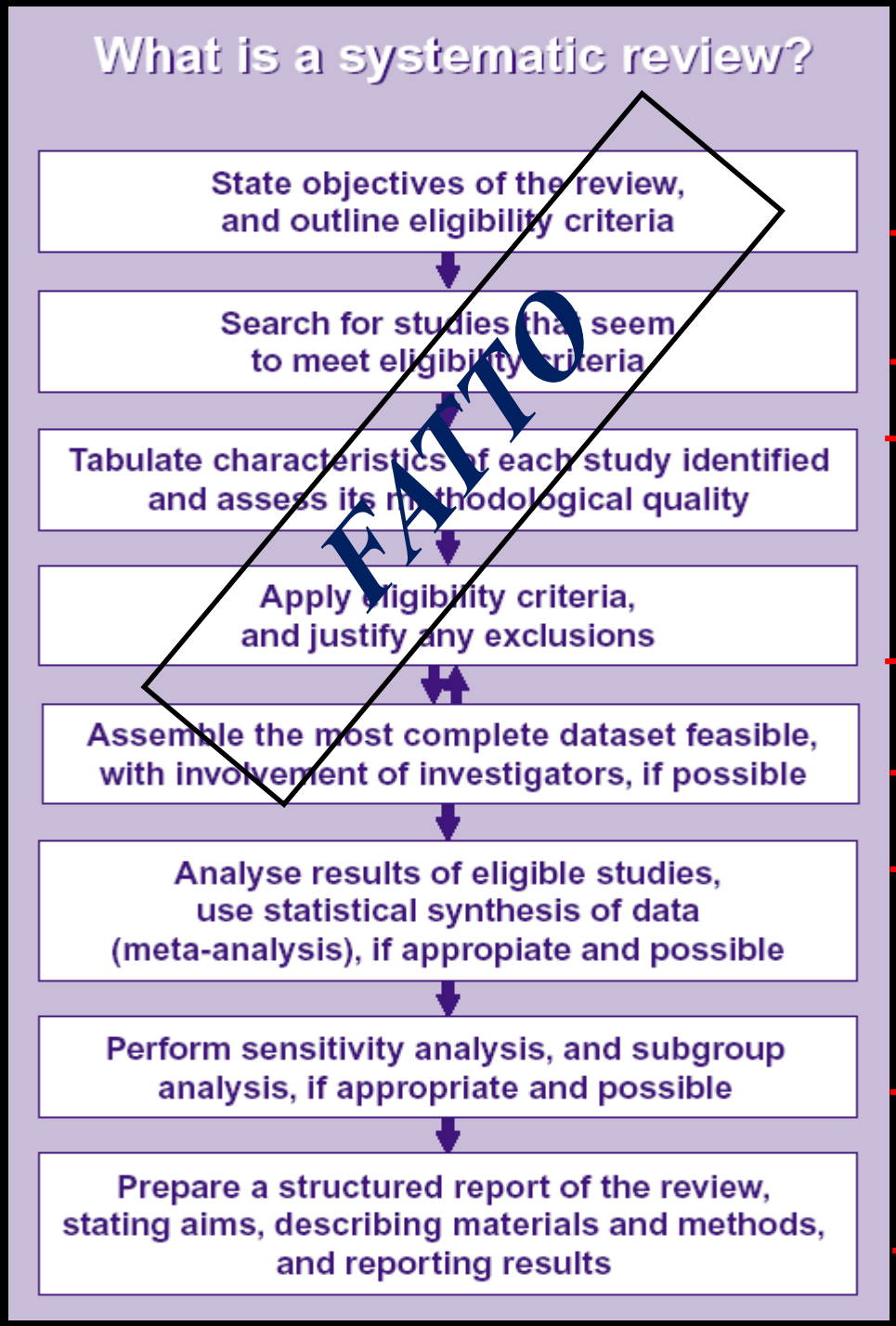
Eterogeneità

Negrar, 7 aprile 2018



I passi di una RS

Definizione del quesito

Ricerca sistematica delle fonti

Valutazione dei criteri di inclusione ed esclusione e della qualità degli studi eleggibili

Ricerca della migliore sintesi qualitativa delle informazioni

Sintesi quantitativa dei risultati (Metanalisi) se fattibile ad appropriata

Scrittura del paper finale

Principi di una meta-analisi

Una **meta-analisi** può:

•Combinare i risultati dei singoli studi per ottenere una stima complessiva dell'effetto del trattamento;

•Esplorare l'eterogeneità tra gli studi (e le relative fonti di eterogeneità).

When can/should you do a meta-analysis?

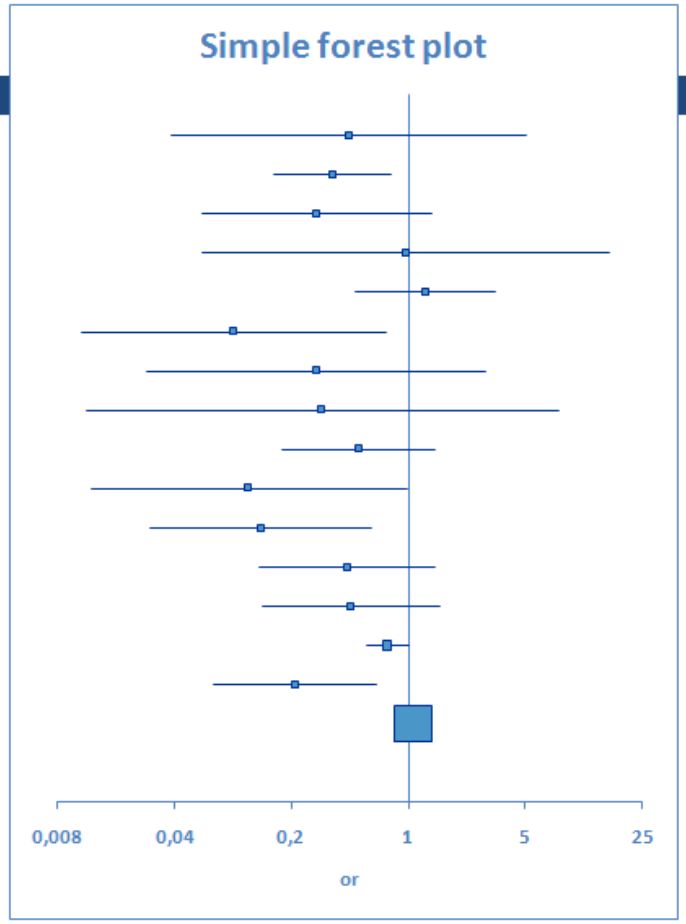
- When more than one study has estimated an effect
- When there are no differences in the study characteristics that are likely to substantially affect outcome
- When the outcome has been measured in similar ways
- When the data are available (take care with interpretation when only some data are available)

E' efficace?

Author(s)		Reference					
Teo et al.		Effects of intravenous magnesium in suspected acute myocardial infarction. BMJ 1991;303:1499–501					
Outcome object	Unit	Intervention (e)		Control (c)			
Mortality	Event	Intravenous magnesium		Control			
Study ID	Ref #	n[e]	n[e](E=1)	n[c]	n[c](E=1)	Study date	-
Morton	1	40	1	36	2	1984	
Rasmussen	2	135	9	135	23	1986	
Smith	3	200	2	200	7	1986	
Abraham	4	48	1	46	1	1987	
Feldstedt	5	150	10	148	8	1988	
Schechter	6	59	1	56	9	1989	
Ceremuzynski	7	25	1	23	3	1989	
Bertschat	8	22	0	21	1	1989	
Singh	9	76	6	75	11	1990	
Pereira	10	27	1	27	7	1990	
Schechter 1	11	89	2	80	12	1991	
Golf	12	23	5	33	13	1991	
Thogersen	13	130	4	122	8	1991	
LIMIT-2	14	1159	90	1157	118	1992	
Schechter 2	15	107	4	108	17	1995	
ISIS-4	16	29011	2216	29039	2103	1995	

Forest plot (meta-graph) analitico

author	year	n[I]	N[I]	n[C]	N[C]	Weight	or	ci-	ci+	p
Morton	1984	1	40	2	36	0,06%	0,44	0,04	5,02	0,51
Rasmussen	1986	9	135	23	135	0,54%	0,35	0,15	0,78	0,01
Smith	1986	2	200	7	200	0,14%	0,28	0,06	1,36	0,11
Abraham	1987	1	48	1	46	0,05%	0,96	0,06	15,77	0,98
Feldstedt	1988	10	150	8	148	0,39%	1,25	0,48	3,26	0,65
Schechter	1989	1	59	9	56	0,08%	0,09	0,01	0,74	0,02
Ceremuzynsk	1989	1	25	3	23	0,07%	0,28	0,03	2,88	0,28
Bertschat	1989	0	22	1	21	0,03%	0,30	0,01	7,88	0,47
Singh	1990	6	76	11	75	0,32%	0,50	0,17	1,43	0,19
Pereira	1990	1	27	7	27	0,08%	0,11	0,01	0,97	0,05
Schechter 1	1991	2	89	12	80	0,15%	0,13	0,03	0,60	0,01
Golf	1991	5	23	13	33	0,24%	0,43	0,13	1,44	0,17
Thogersen	1991	4	130	8	122	0,24%	0,45	0,13	1,54	0,21
LIMIT-2	1992	90	1159	118	1157	4,33%	0,74	0,56	0,99	0,04
Schechter 2	1995	4	107	17	108	0,28%	0,21	0,07	0,64	0,01
ISIS-4	1995	2216	29011	2103	29039	92,99%	1,06	1,00	1,13	0,07



META-ANALYSIS

General

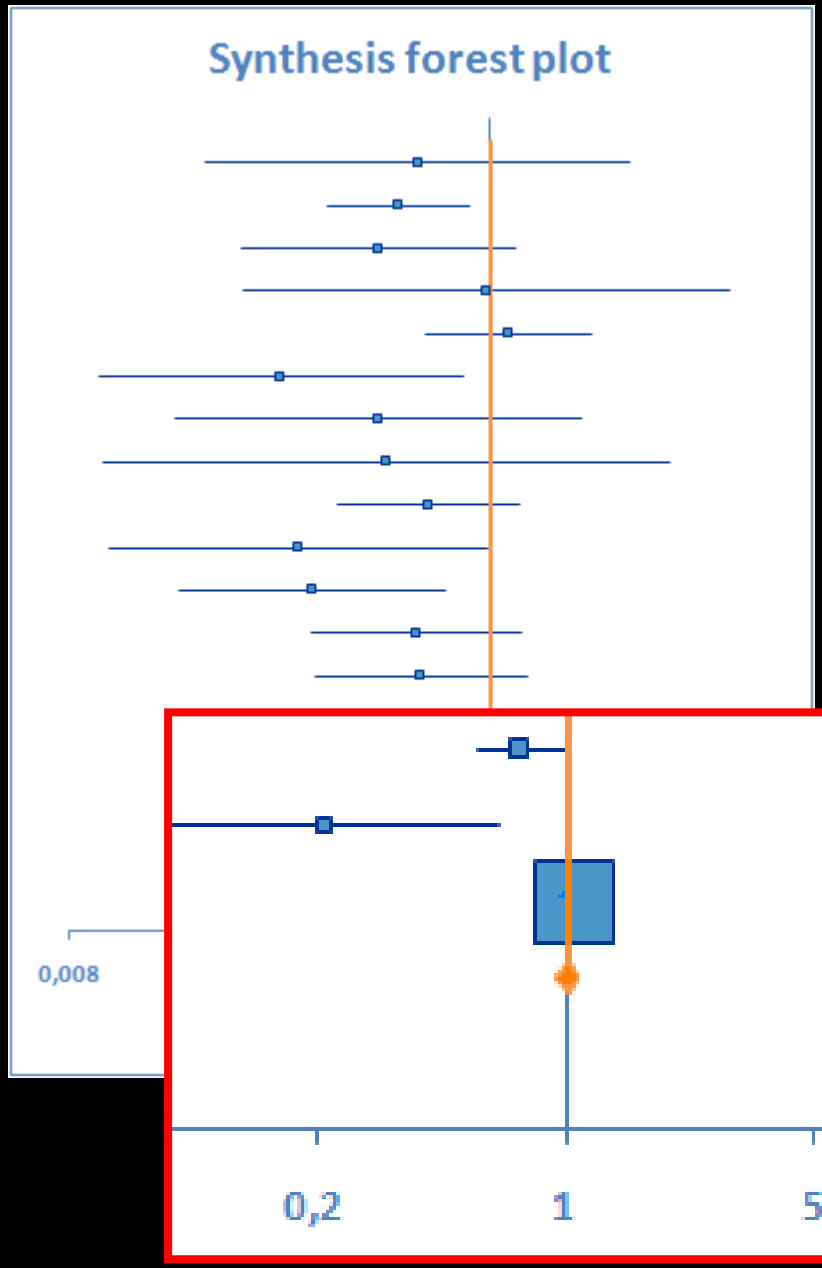
Number of studies	16
Number of participants	62607 (62607)

OR (MH) - Fixed effect model

Meta-analysis outcome	1,0063
95% CI lower limit	0,9482
95% CI upper limit	1,068
z	0,2073
p-value (two-tailed)	0,8358

Heterogeneity

Q	47,1363
p-value (two-tailed)	< 0,0001
I^2	68,18%
95% CI lower limit	46,53%
95% CI upper limit	81,06%



Could we just add the data from all the trials together?

- One approach to combining trials would be to add all the treatment groups together, add all the control groups together, and compare the totals
- This is wrong for several reasons, and it can give the wrong answer

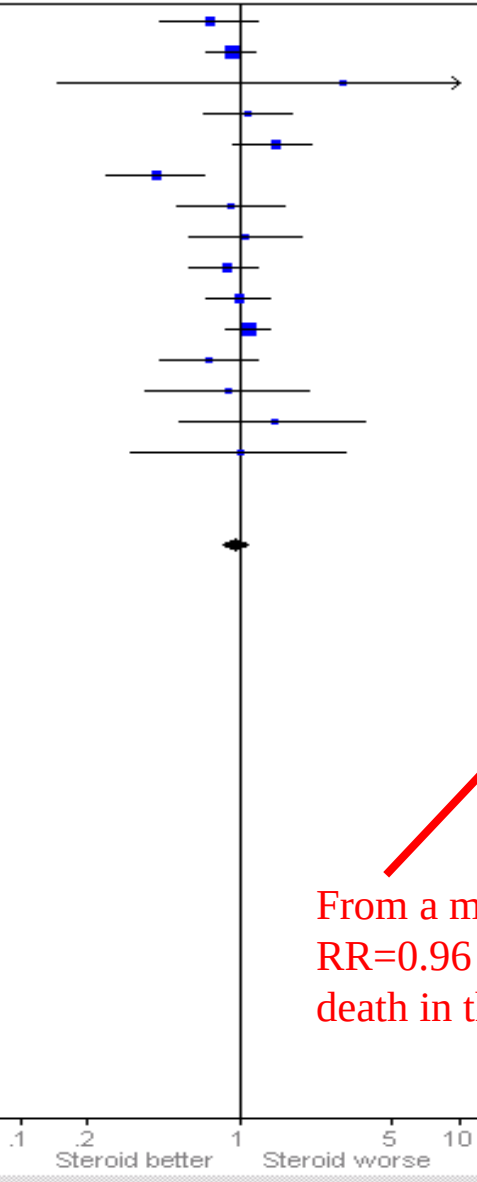
MetaView 3.1 - [Death at end of follow up period (Corticosteroids for acute traumatic brain injury)]

File Display Sort Statistic Window Next Outcome Prev Outcome

Comparison: Any steroid administered in any dose against no steroid
Outcome: Death at end of follow up period

Study	Expt n/N	Ctrl n/N	Weight %	RR (95%CI Fixed)
Alexander 1972	16 / 55	22 / 55	6.6	0.73 [0.43,1.23]
Braakman 1983	44 / 81	47 / 80	14.2	0.92 [0.70,1.21]
Chacon 1987	1 / 5	0 / 5	0.2	3.00 [0.15,59.89]
Cooper 1979	26 / 49	13 / 27	5.0	1.10 [0.69,1.77]
Dearden 1986	33 / 68	21 / 62	6.6	1.43 [0.94,2.19]
Faupel 1976	16 / 67	16 / 28	6.8	0.42 [0.24,0.71]
Gaab 1994	19 / 133	21 / 136	6.2	0.93 [0.52,1.64]
Giannotta 1984	34 / 72	7 / 16	3.4	1.08 [0.59,1.98]
Grumme 1995	38 / 175	49 / 195	13.9	0.86 [0.60,1.25]
Hernesniemi 1979	35 / 81	36 / 83	10.7	1.00 [0.70,1.41]
Pitts 1980	114 / 201	38 / 74	16.7	1.10 [0.86,1.42]
Ransohoff 1972	9 / 17	13 / 18	3.8	0.73 [0.43,1.25]
Saul 1981	8 / 50	9 / 50	2.7	0.89 [0.37,2.12]
Stubbs 1989	13 / 98	5 / 54	1.9	1.43 [0.54,3.80]
Zagara 1987	4 / 12	4 / 12	1.2	1.00 [0.32,3.10]
xZarate 1995	0 / 30	0 / 30	0.0	Not Estimable
Total (95%CI)	410 / 1194	301 / 925	100.0	0.96 [0.85,1.08]

Chi-square 18.11 (df=14) Z=0.68



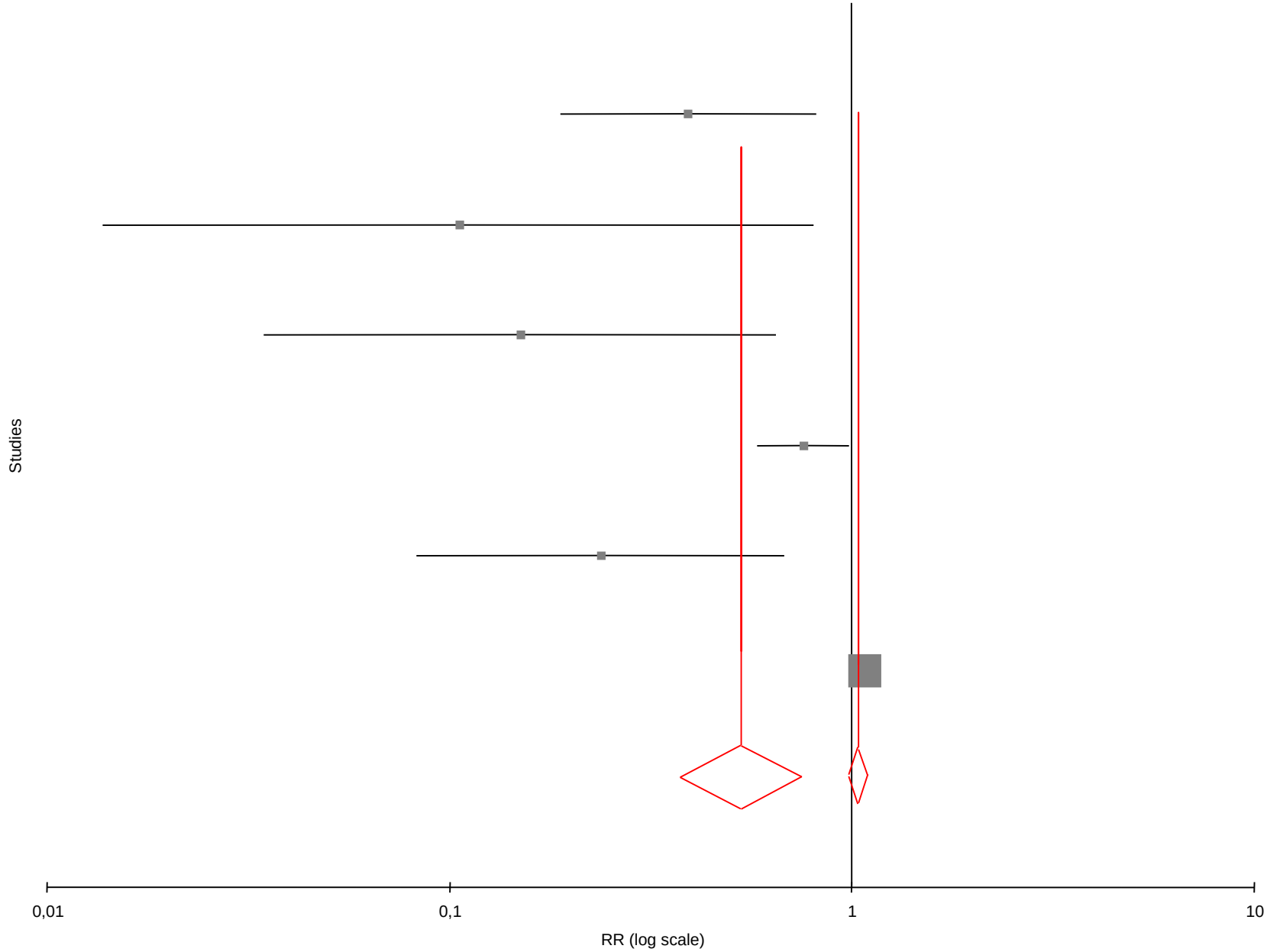
If we add up the columns we get 34.3% vs 32.5% , a RR of 1.06, a higher chance of death in the steroids group

From a meta-analysis, we get RR=0.96 , a lower chance of death in the steroids group

L'intervento funziona?

Valore neutro ("nullo")	Esito sfavorevole (es. morte)	Esito favorevole (es. smettere di fumare)	Effetto avverso (es. vomito)
L'intervento non ha effetto	L'intervento funziona	L'intervento funziona	L'intervento funziona
RD = 0	RD < 0	RD > 0	RD < 0
RR = 1	RR < 1	RR > 1	RR < 1
OR = 1	OR < 1	OR > 1	OR < 1

RD: Risk Difference **RR: Relative Risk** **OR: Odds Ratio**


Studies
0,01
0,1
1
10
RR (log scale)

Come si decide quanto pesa uno studio?

- Il peso è proporzionale al contributo informativo dello studio alla capacità di effettuare una stima
- Studi di ampie dimensione e/o con molti eventi potrebbero contribuire di più
- In gergo sono quelli più precisi

- Ma tutto è relativo … tutti gli studi stanno misurando lo stesso effetto?

What is heterogeneity?

- Heterogeneity is variation between the studies' results

What is heterogeneity?

Differences between studies with respect to:

Clinical heterogeneity (clinical diversity)

- *Participants*
  - e.g. conditions under investigation, eligibility criteria for trials, geographical variation
- *Interventions*
  - e.g. intensity / dose / duration, sub-type of drug, mode of administration, experience of practitioners, nature of the control (placebo/none/standard care)
- *Outcomes*
  - e.g. definition of an event, follow-up duration, ways of measuring outcomes, cut-off points on scales

What is heterogeneity?

Differences between studies with respect to:

Methodological heterogeneity (methodological diversity)

- *Design*
  - e.g. randomised vs non-randomised, crossover vs parallel group vs cluster randomised, pre-test and long follow up
- *Conduct*
  - e.g. allocation concealment, blinding etc, approach to analysis, imputation methods for missing data

What is heterogeneity?

What do we do if there ***is*** statistical heterogeneity?

- Variation in the *true effects* underlying the studies
- ...which may manifest itself in more observed variation than expected by chance alone

- May be due to clinical diversity (different treatment effects) or methodological diversity (different biases)

Come si misura questa eterogeneità?

- Confidence interval overlapping Eyeball test

- Cochran's Q: to assess whether observed differences in results are compatible with change alone

χ^2 distribution; low power (small number of studies, small sample size)

p=<0.10 (heterogeneity)

- I^2 quantifing heterogeneity (describes the percentage of variation across studies that is due to heterogeneity rather than chance)

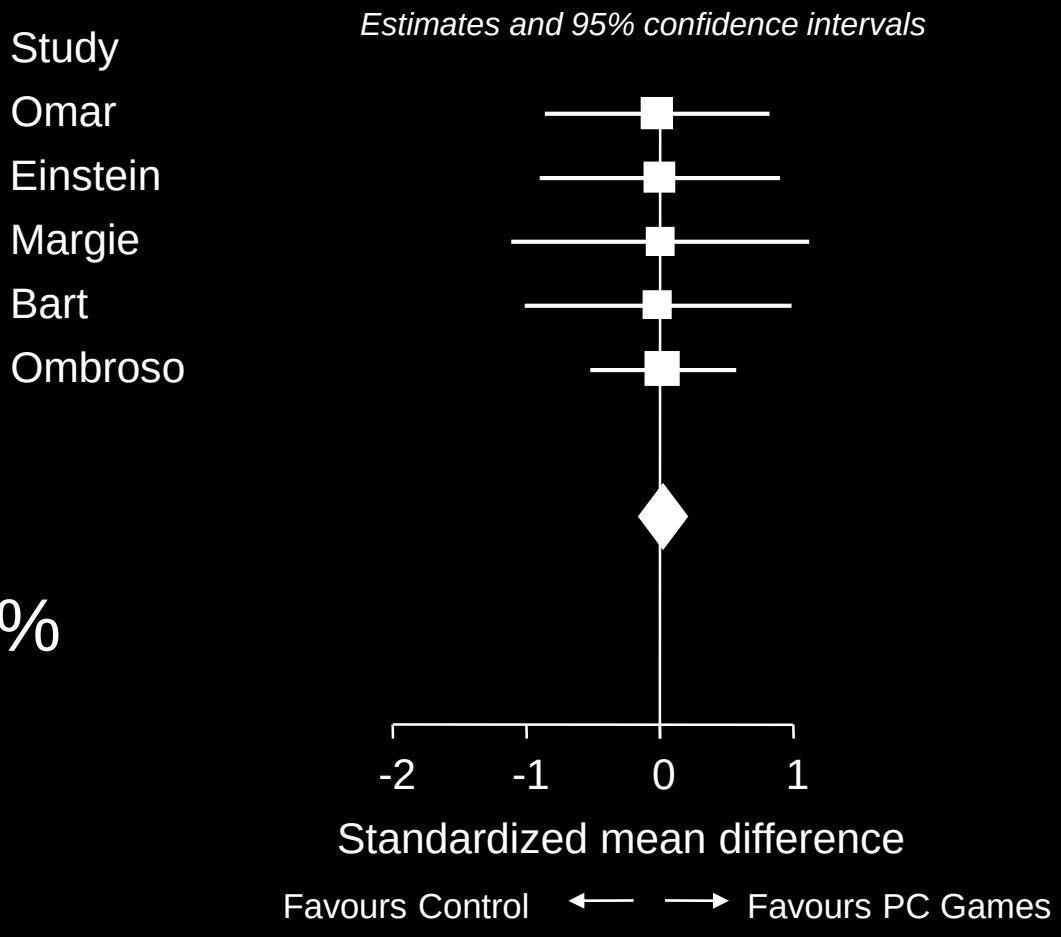
0-40% might not be important
30-60% may represent moderate heterogeneity
50-90% may represent substantial heterogeneity
75-100% considerable heterogeneity

- Tau….

How to deal with heterogeneity

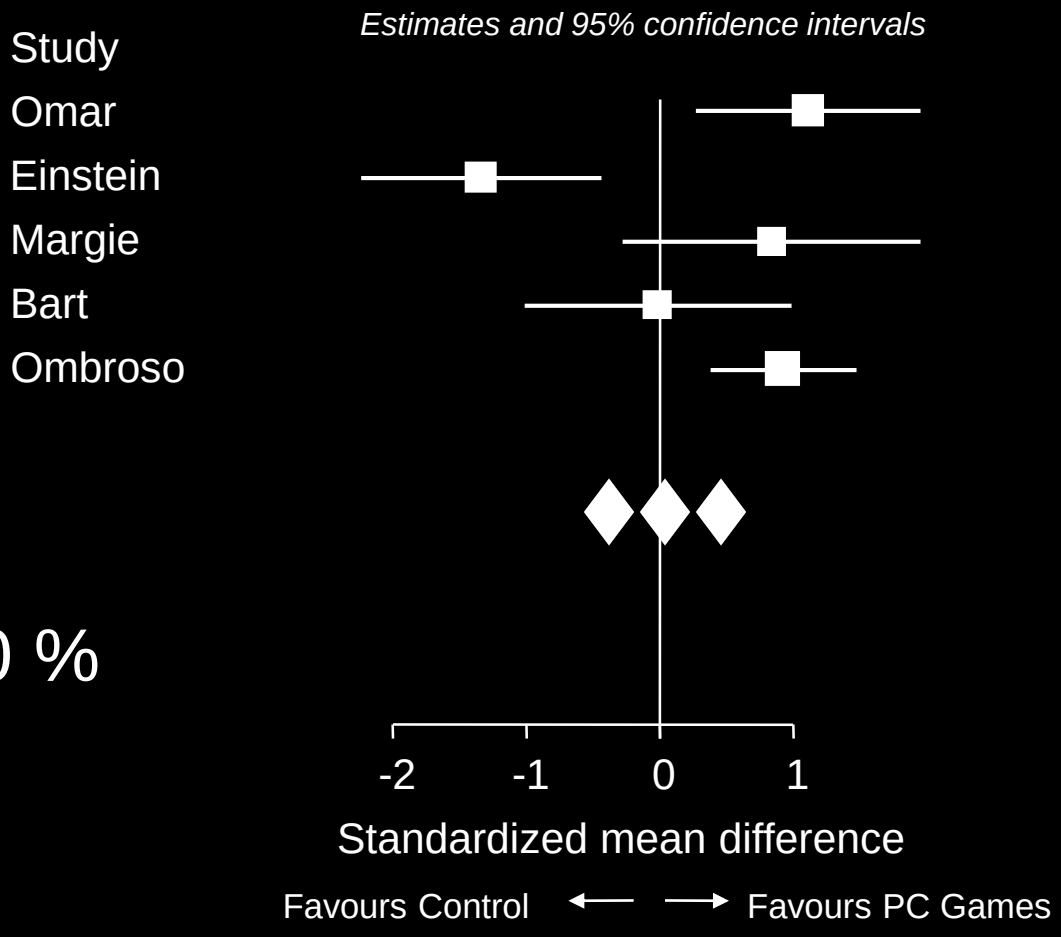
1. Do not pool at all
2. Ignore heterogeneity: use ***fixed effect model***
3. Allow for heterogeneity: use ***random effects model***
4. Explore heterogeneity: subgroups analysis or meta-regression (tricky)

Example: PC Games for intelligence



$I^2 = 0\ \%$

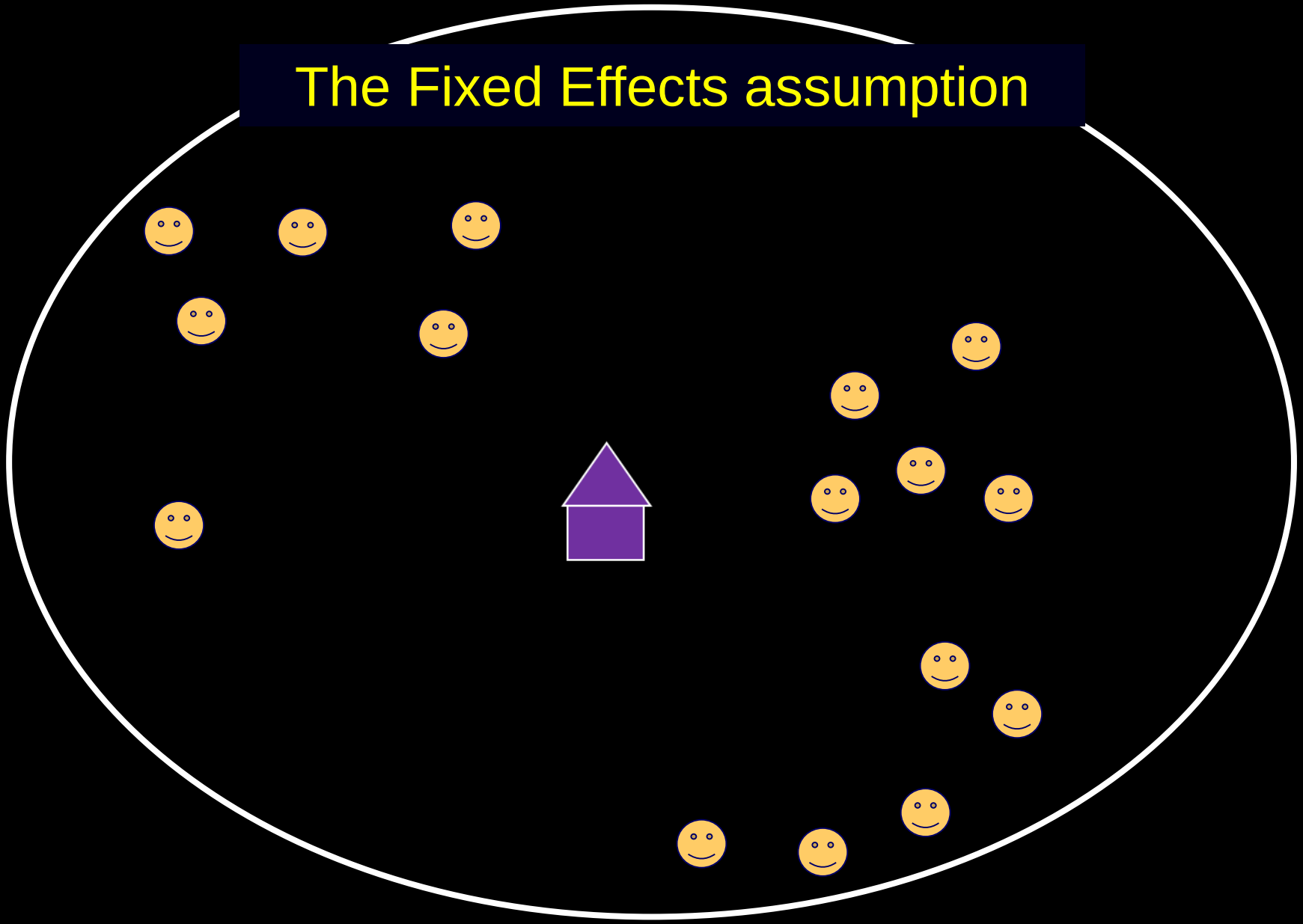
Example: PC Games for intelligence



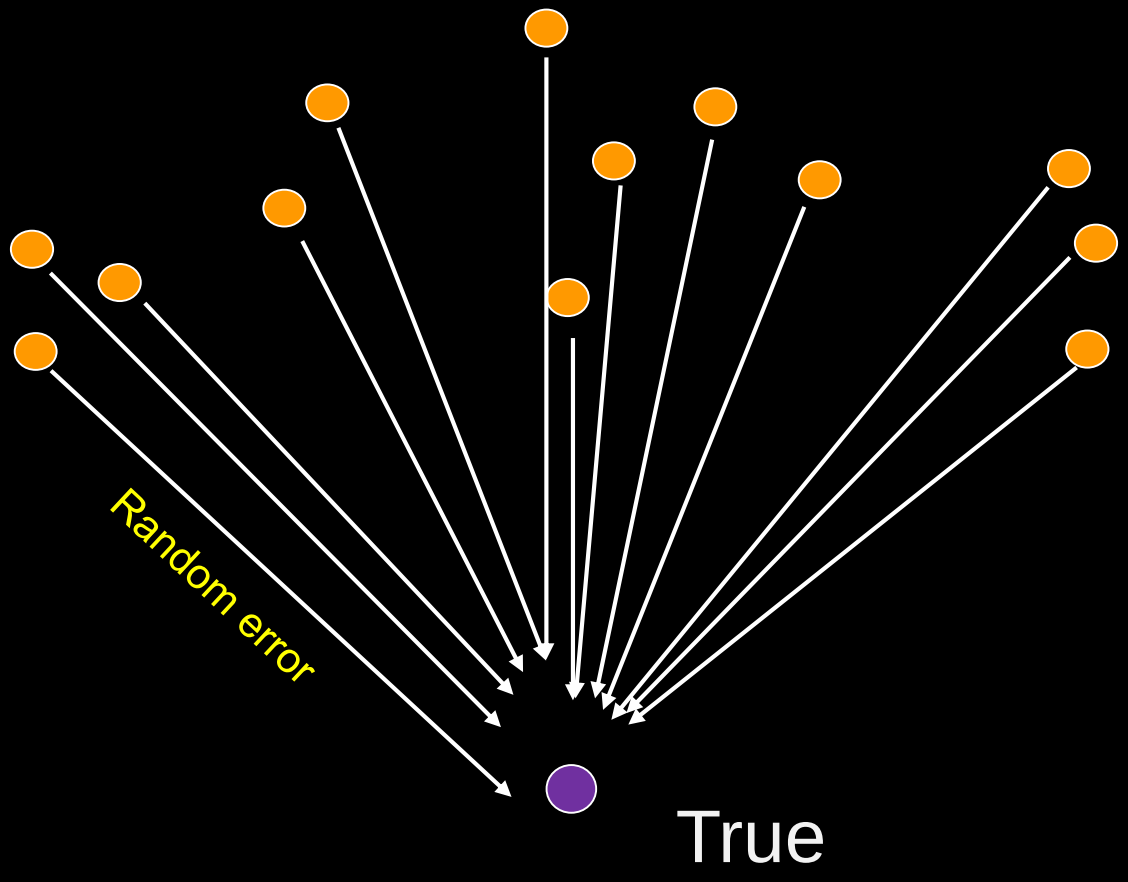
$I^2 = 80\ \%$

Fixed and random effects

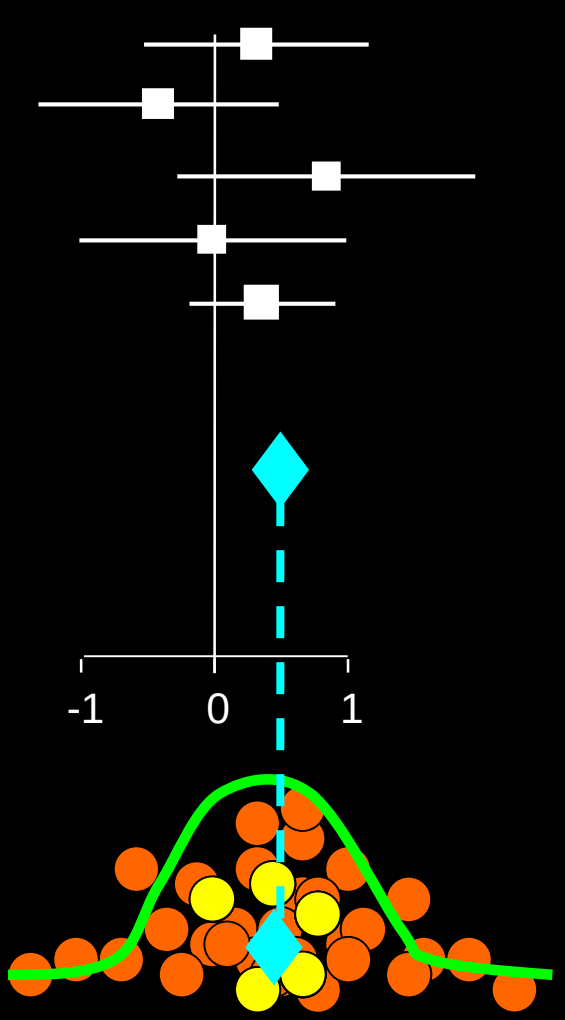
The Fixed Effects assumption



The Fixed Effects assumption



Fixed effects model



In un modello a effetti fissi si assume che tutti gli studi provengano dalla stessa popolazione di studi

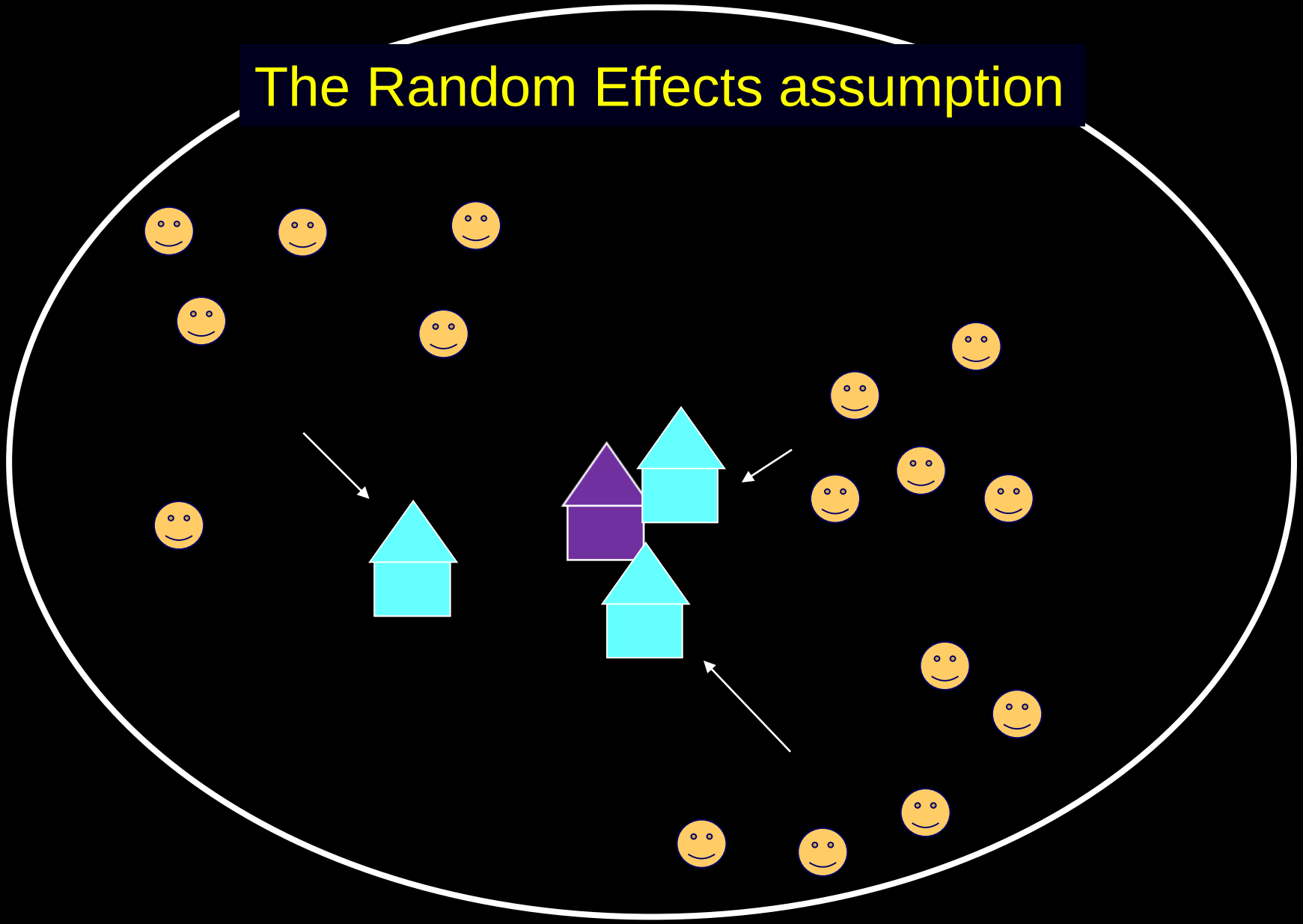
Si assume che ci sia un parametro (es.media) unico, fisso

Il peso degli studi è funzione della variabilità intra-studio

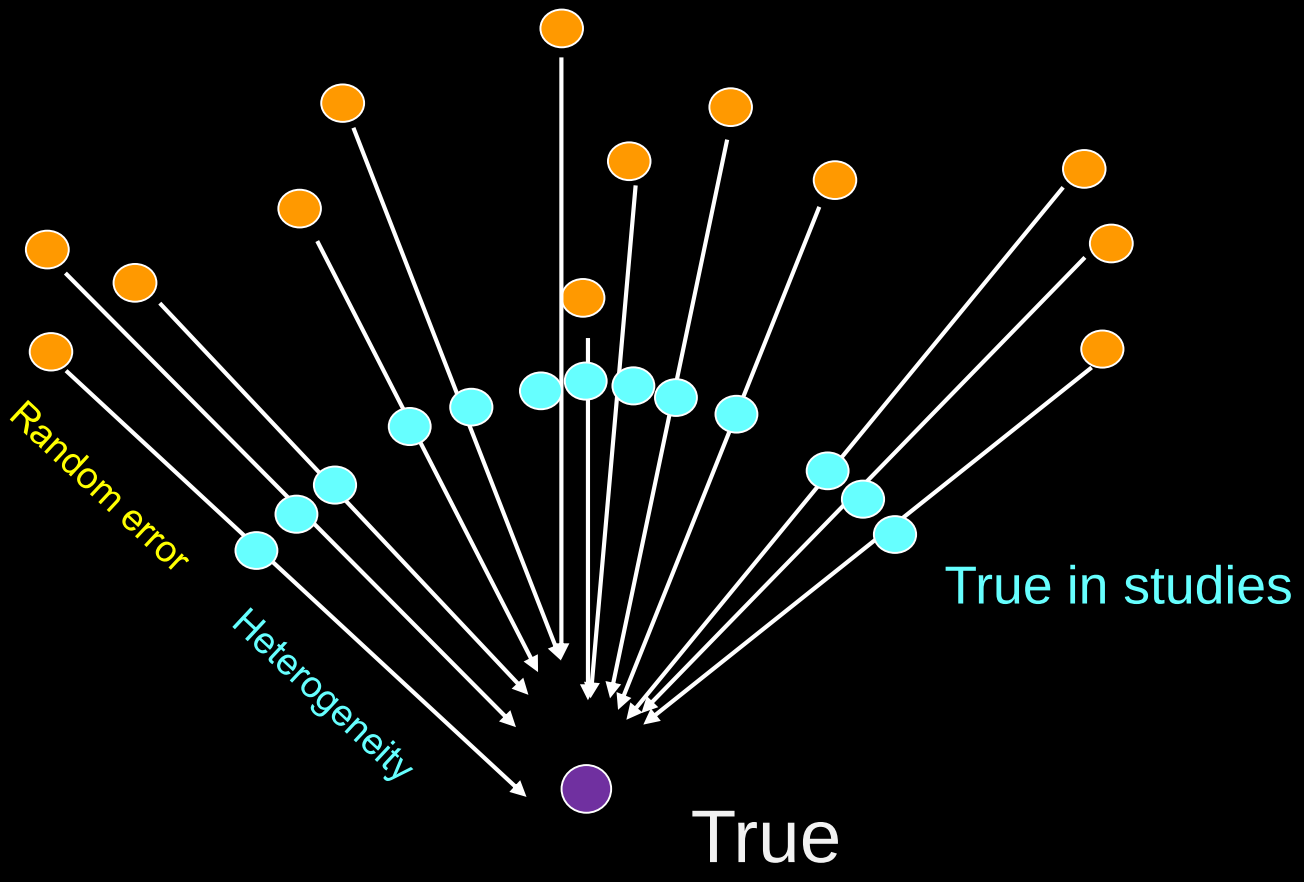
Gli intervalli di confidenza del parametro sono ridotti

Popolazione di riferimento unica, omogenea

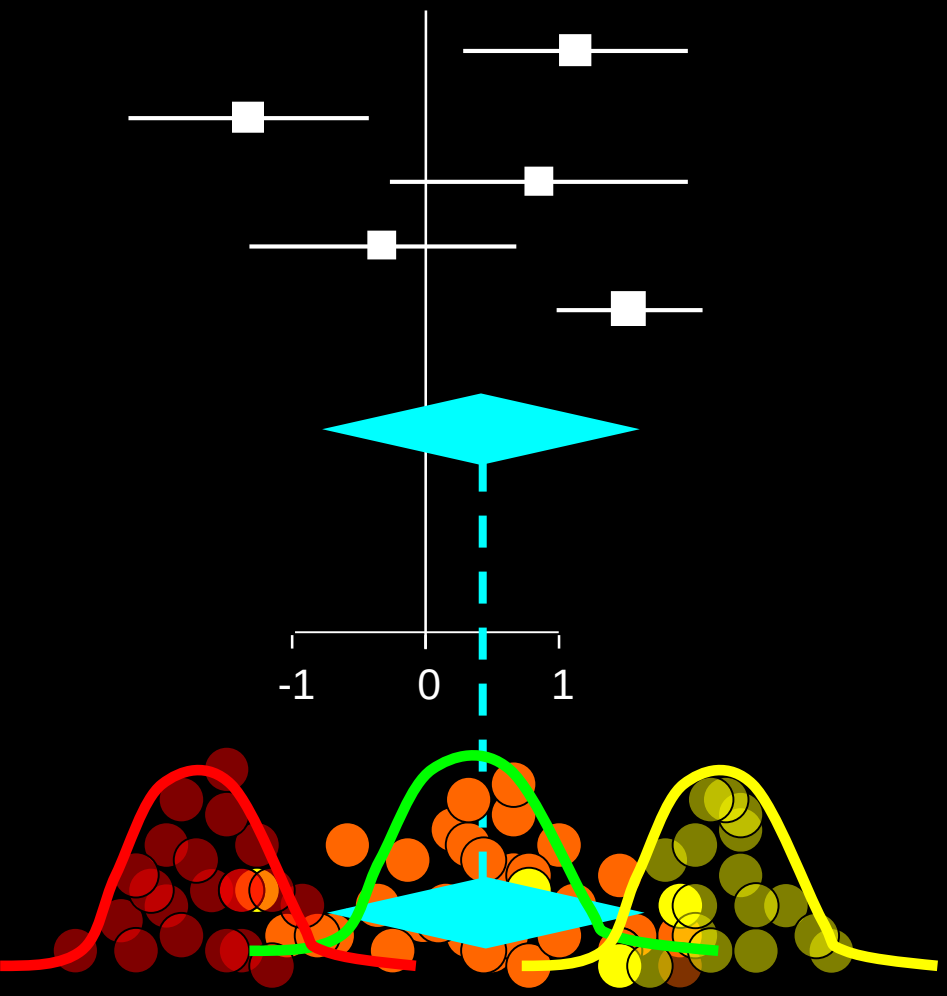
The Random Effects assumption



The Random Effects assumption



Random effects model



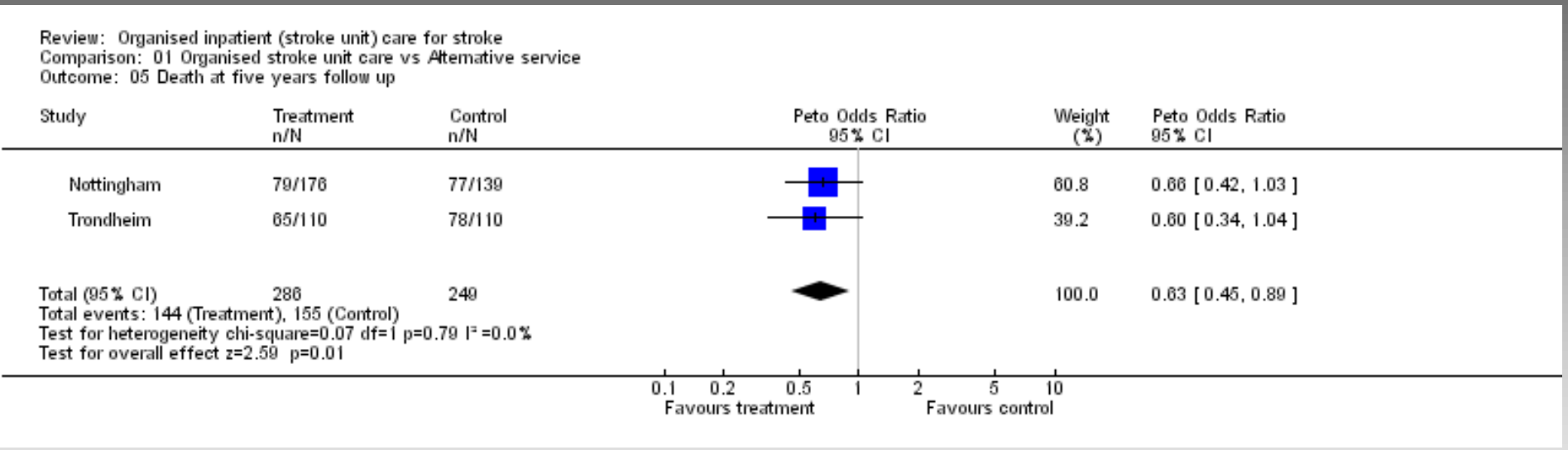
In un modello a effetti random gli studi potrebbero provenire da popolazioni di studi diverse

I pesi sono ridistribuiti in modo più omogeneo tra studi grandi e piccoli (il peso non è dovuto solo alla variabilità intra-studio)

Gli intervalli di confidenza del parametro sono aumentati

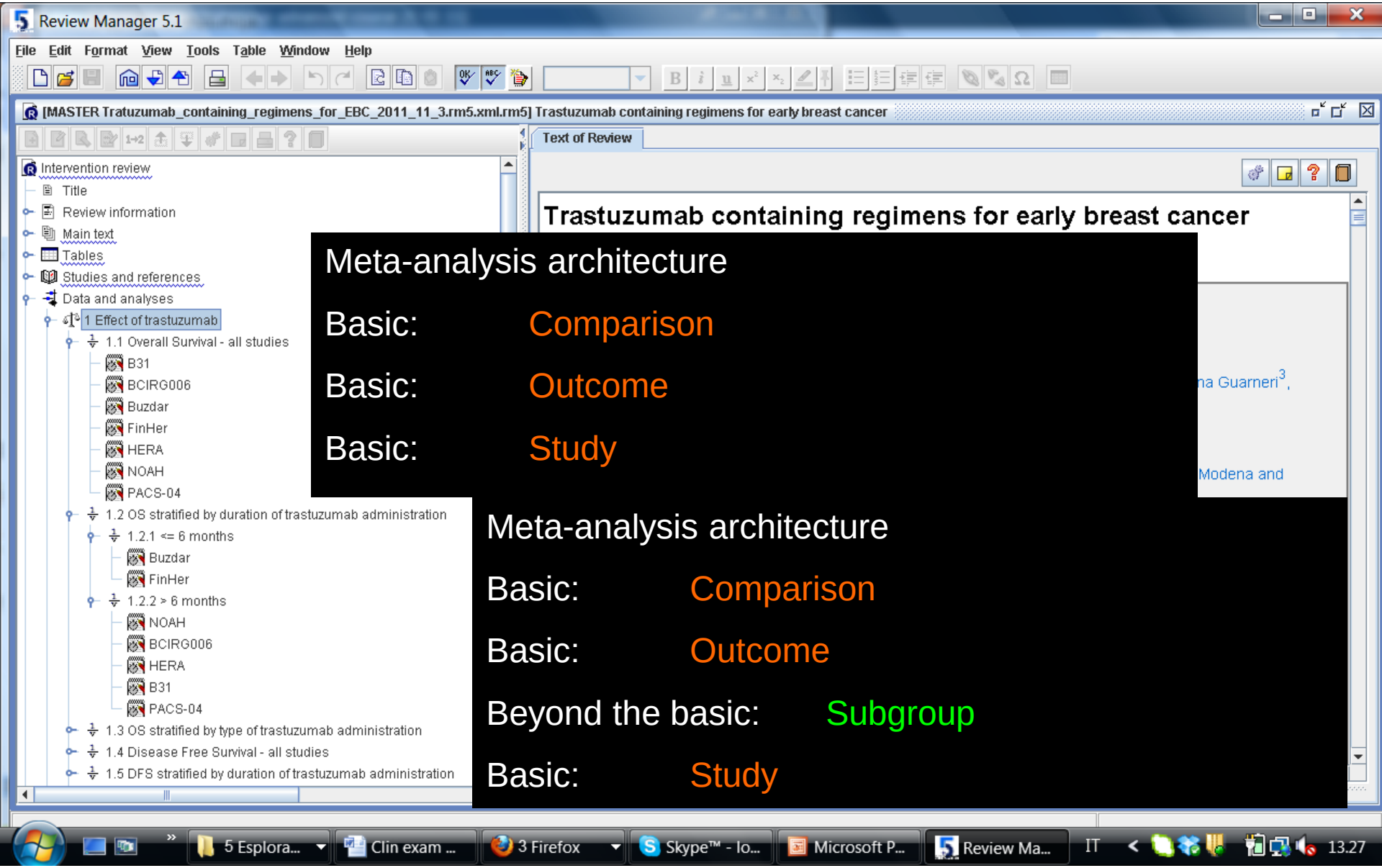
Popolazioni di riferimento molteplici, eterogenee

Esempio di Metaview



SOTTOGRUPPI


LEGO
Architecture
FRANK LLOYD WRIGHT
COLLECTION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Text of Review
Intervention review
Title
Review information
Main text
Tables
Studies and references
Data and analyses
1 Effect of trastuzumab
1.1 Overall Survival - all studies
B31
BCIRG006
Buzdar
FinHer
HERA
NOAH
PACS-04
1.2 OS stratified by duration of trastuzumab administration
1.2.1 <= 6 months
Buzdar
FinHer
1.2.2 > 6 months
NOAH
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PACS-04
1.3 OS stratified by type of trastuzumab administration
1.4 Disease Free Survival - all studies
1.5 DFS stratified by duration of trastuzumab administration
Trastuzumab containing regimens for early breast cancer
Meta-analysis architecture
Basic: Comparison
Basic: Outcome
Basic: Study
Meta-analysis architecture
Basic: Comparison
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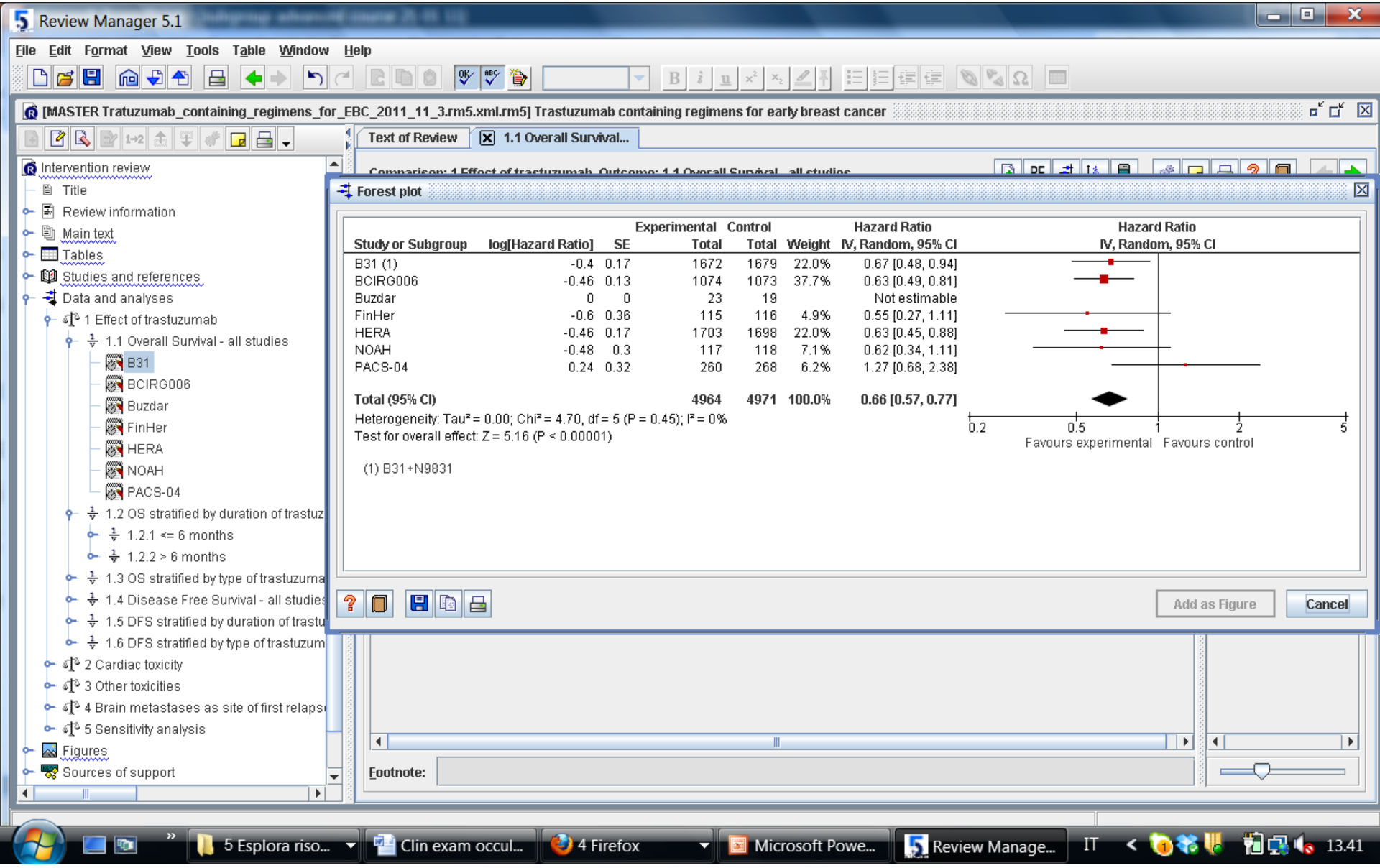
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1.5 DFS stratified by duration of trastu
1.6 DFS stratified by type of trastuzum
2 Cardiac toxicity
3 Other toxicities
4 Brain metastases as site of first relaps
5 Sensitivity analysis
Figures
Sources of support
Forest plot
Experimental
Control
Hazard Ratio
Hazard Ratio
Study or Subgroup log[Hazard Ratio] SE Total Total Weight IV, Random, 95% CI
IV, Random, 95% CI
B31 (1) -0.4 0.17 1672 1679 22.0% 0.67 [0.48, 0.94]
BCIRG006 -0.46 0.13 1074 1073 37.7% 0.63 [0.49, 0.81]
Buzdar 0 0 23 19 Not estimable
FinHer -0.6 0.36 115 116 4.9% 0.55 [0.27, 1.11]
HERA -0.46 0.17 1703 1698 22.0% 0.63 [0.45, 0.88]
NOAH -0.48 0.3 117 118 7.1% 0.62 [0.34, 1.11]
PACS-04 0.24 0.32 260 268 6.2% 1.27 [0.68, 2.38]
Total (95% CI) 4964 4971 100.0% 0.66 [0.57, 0.77]
Heterogeneity: Tau² = 0.00; Chi² = 4.70, df = 5 (P = 0.45); I² = 0%
Test for overall effect: Z = 5.16 (P < 0.00001)
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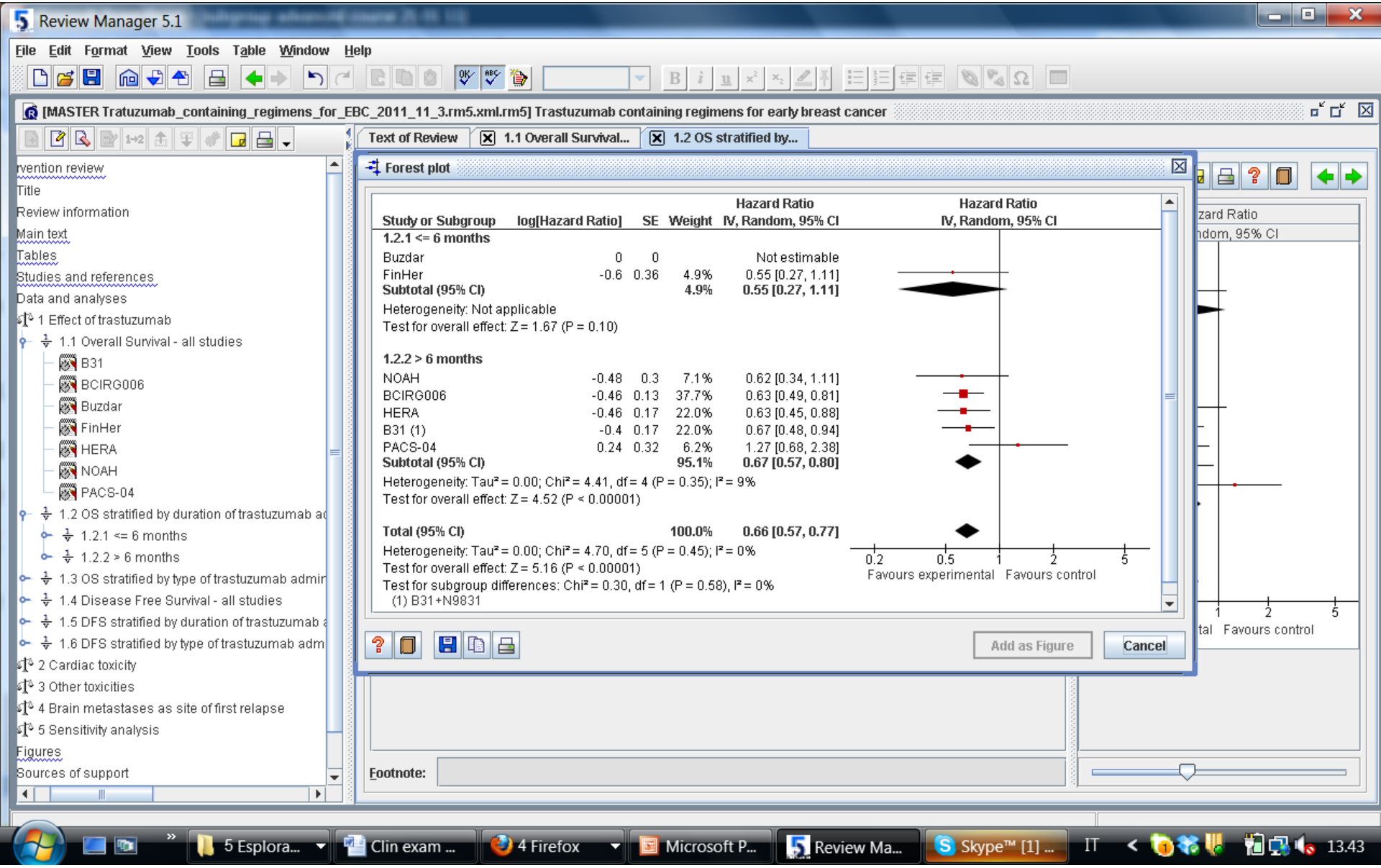
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1.2 OS stratified by...
Forest plot
Study or Subgroup log[Hazard Ratio] SE Weight Hazard Ratio IV, Random, 95% CI
Hazard Ratio IV, Random, 95% CI
1.2.1 <= 6 months
Buzdar 0 0 Not estimable
FinHer -0.6 0.36 4.9% 0.55 [0.27, 1.11]
Subtotal (95% CI) 4.9% 0.55 [0.27, 1.11]
Heterogeneity: Not applicable
Test for overall effect: Z = 1.67 (P = 0.10)
1.2.2 > 6 months
NOAH -0.48 0.3 7.1% 0.62 [0.34, 1.11]
BCIRG006 -0.46 0.13 37.7% 0.63 [0.49, 0.81]
HERA -0.46 0.17 22.0% 0.63 [0.45, 0.88]
B31 (1) -0.4 0.17 22.0% 0.67 [0.48, 0.94]
PACS-04 0.24 0.32 6.2% 1.27 [0.68, 2.38]
Subtotal (95% CI) 95.1% 0.67 [0.57, 0.80]
Heterogeneity: Tau² = 0.00; Chi² = 4.41, df = 4 (P = 0.35); I² = 9%
Test for overall effect: Z = 4.52 (P < 0.00001)
Total (95% CI) 100.0% 0.66 [0.57, 0.77]
Heterogeneity: Tau² = 0.00; Chi² = 4.70, df = 5 (P = 0.45); I² = 0%
Test for overall effect: Z = 5.16 (P < 0.00001)
Test for subgroup differences: Chi² = 0.30, df = 1 (P = 0.58), I² = 0%
(1) B31+N9831
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Footnote:
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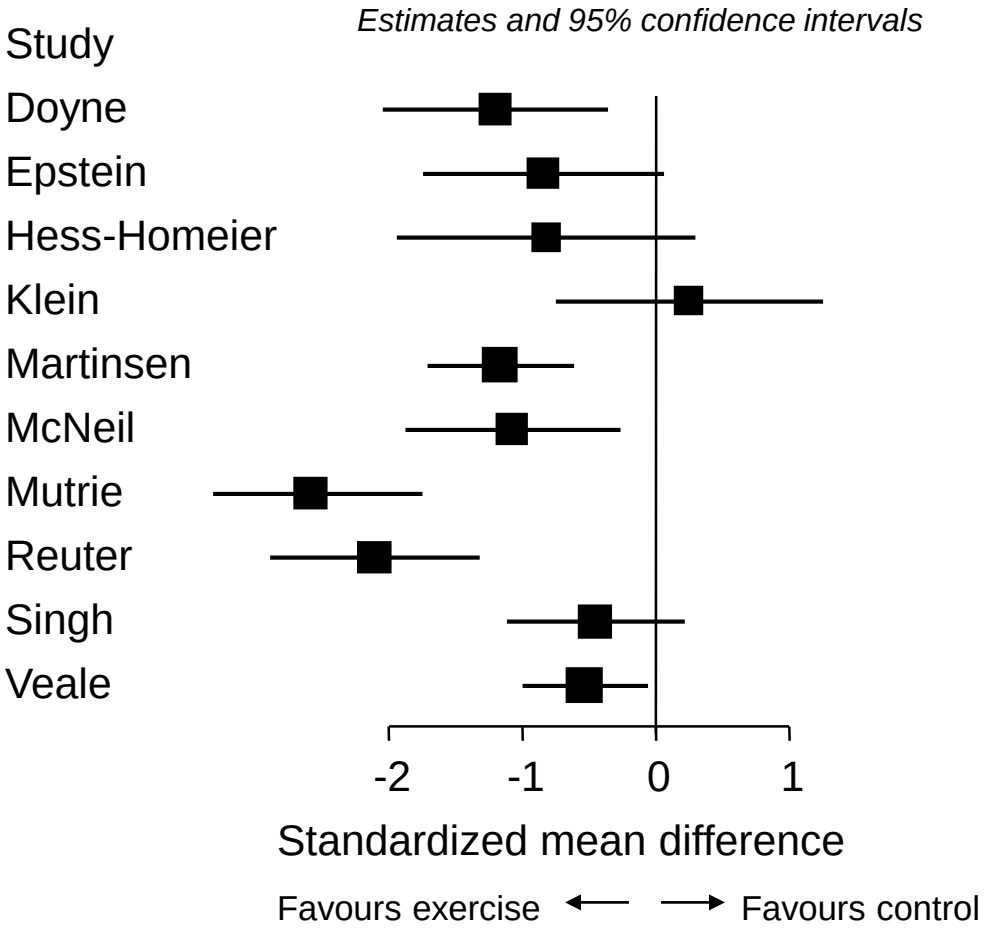
What are subgroup / sensitivity analyses?

- An analysis of treatment effects within subgroups of patients enrolled on a clinical trial who might be expected to respond to treatment differently
- "Should all patients be given XYZ? Can/should treatment be limited to a selected group?"
- Methods for investigating possible causes of heterogeneity in a meta-analysis

•*Only one thing is worse than doing subgroup analyses---believing the results* R. Peto

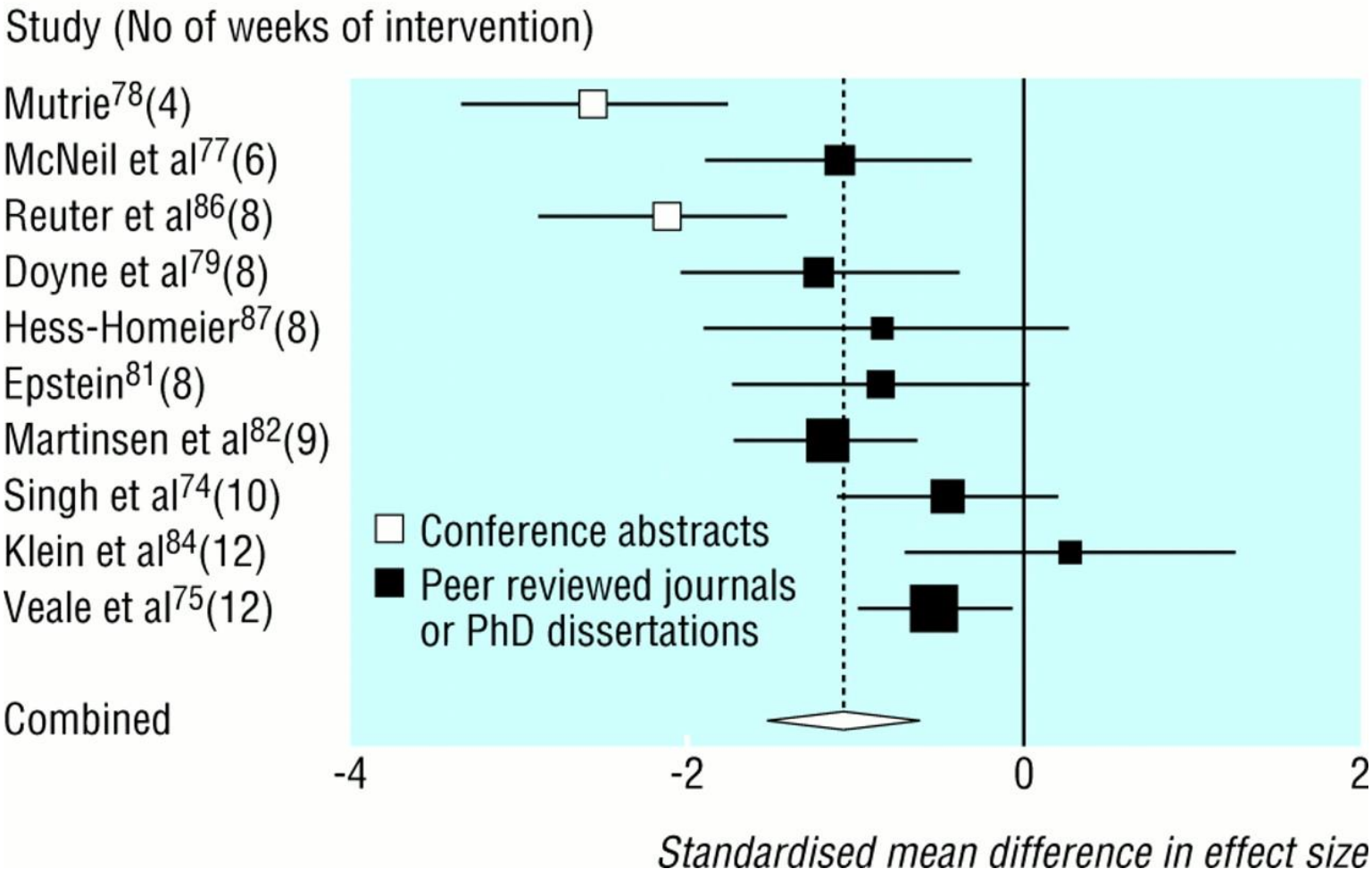
Example: exercise for depression



Lawlor DA, Hopker SW.
BMJ 2001; 322: 763-7

Significant heterogeneity between studies (Q=35.0, P<0.001)

Standardised mean difference in size of effect of exercise compared with "no treatment" for depression.



Lawlor D A , Hopker S W BMJ 2001;322:763

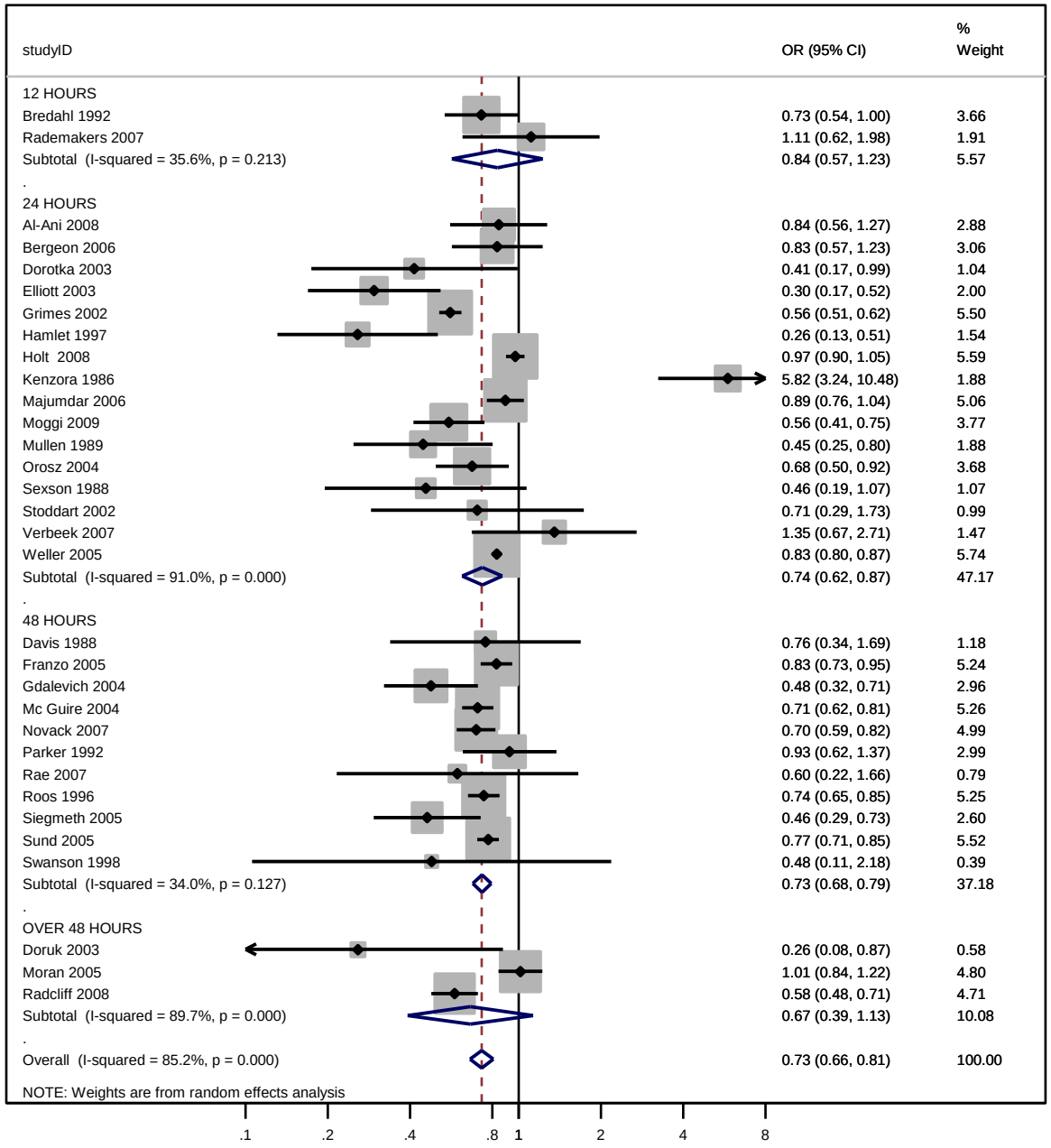
Not associated with

- Allocation concealment
- Intention to treat analysis
- Blinding
- Setting
- Baseline severity of depression
- Or exercise type

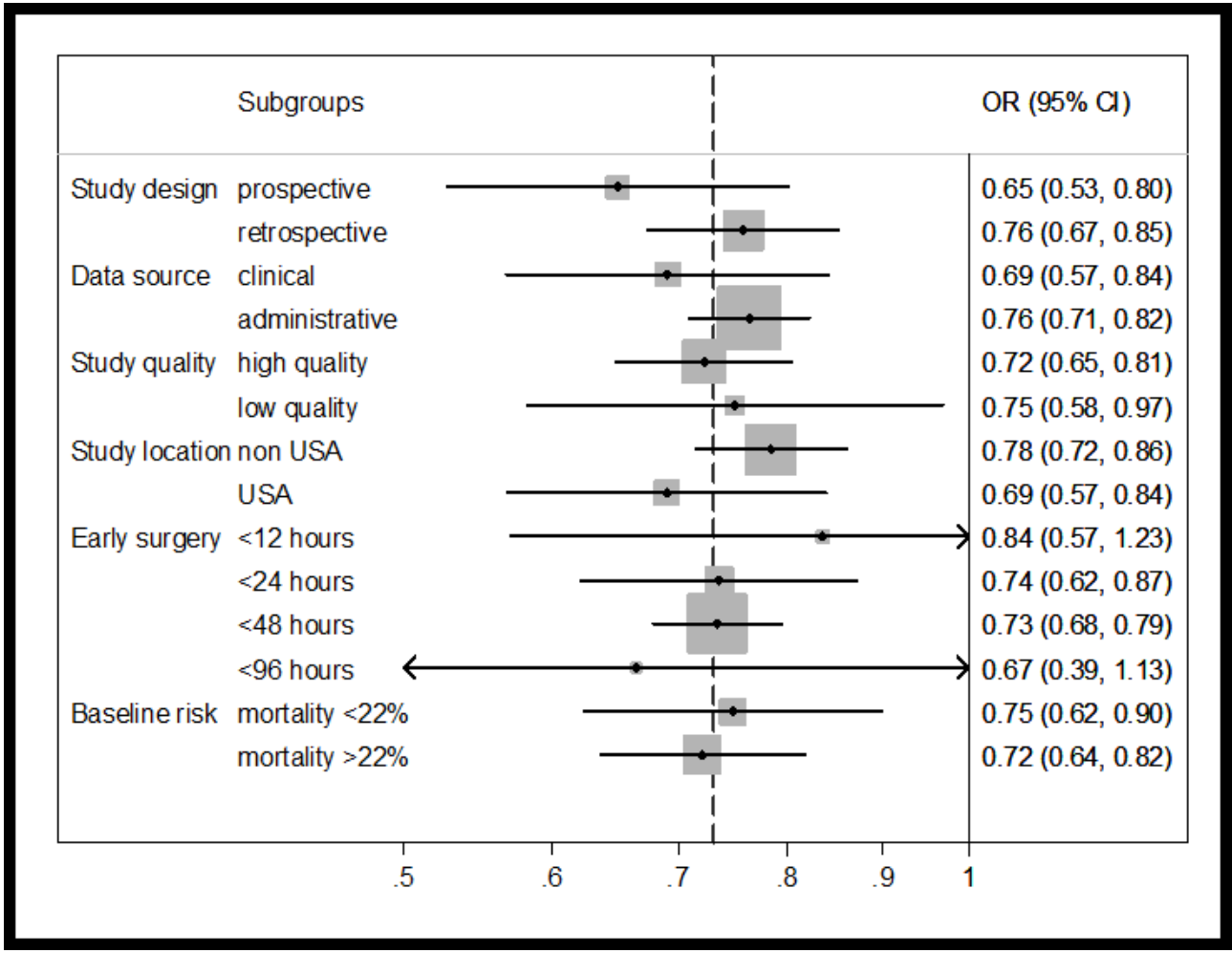
Associated with

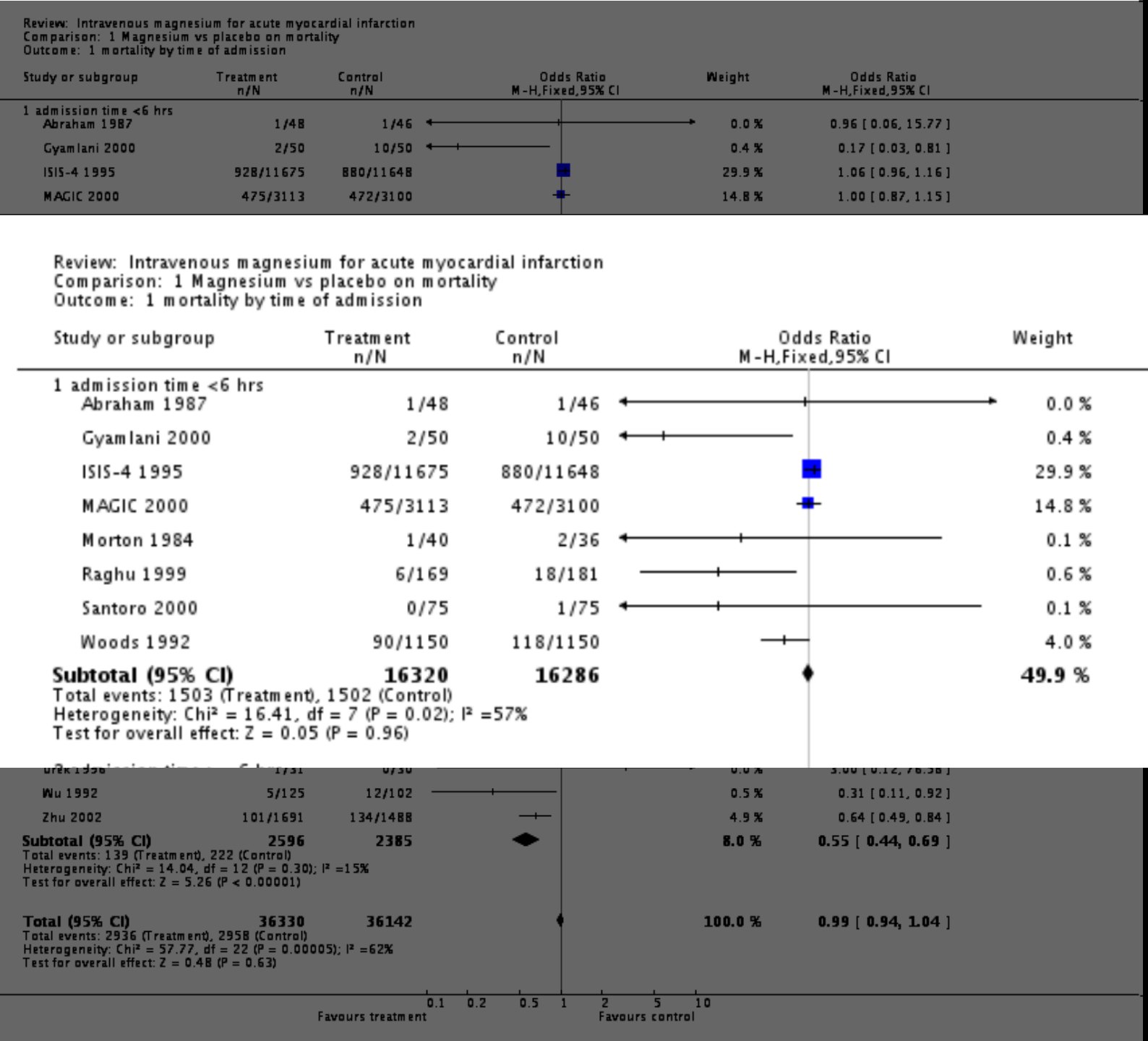
- Type of publication
- Length of follow up.

Meta-analysis of Early versus Delayed surgery time according to cut-off points (12, 24, 48, and over 48 hours). Outcome: overall mortality.

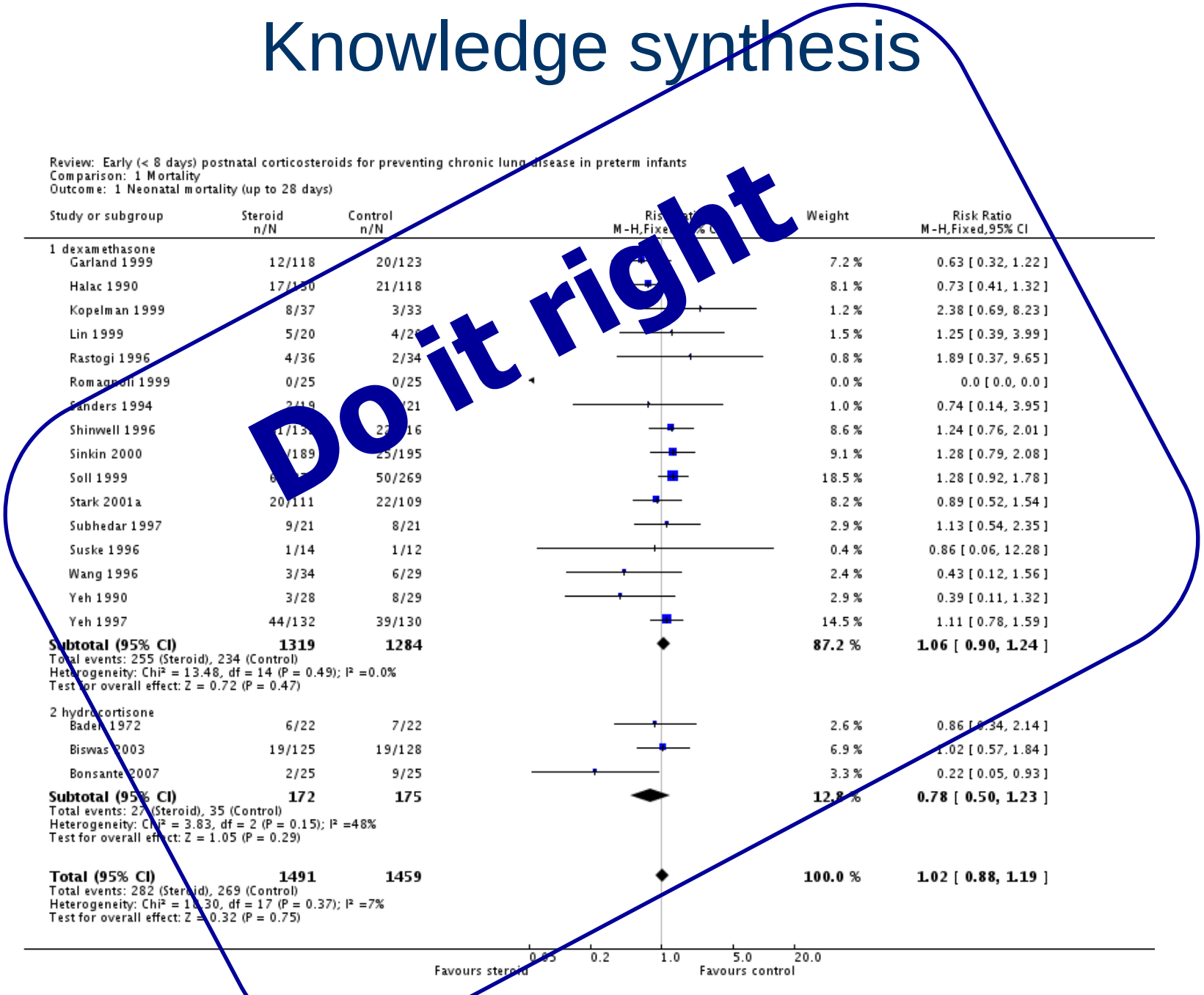


Subgroups analyses of Early and Delayed surgery time for overall mortality.




Review: Intravenous magnesium for acute myocardial infarction
Comparison: 1 Magnesium vs placebo on mortality
Outcome: 1 mortality by time of admission
Study or subgroup
Treatment n/N
Control n/N
Odds Ratio M-H,Fixed,95% CI
Weight
Odds Ratio M-H,Fixed,95% CI
1 admission time <6 hrs
Abraham 1987 1/48 1/46 0.0 % 0.96 [0.06, 15.77]
Gyamlani 2000 2/50 10/50 0.4 % 0.17 [0.03, 0.81]
ISIS-4 1995 928/11675 880/11648 29.9 % 1.06 [0.96, 1.16]
MAGIC 2000 475/3113 472/3100 14.8 % 1.00 [0.87, 1.15]
Morton 1984 1/40 2/36 0.1 % 0.44 [0.04, 5.02]
Raghu 1999 6/169 18/181 0.6 % 0.33 [0.13, 0.86]
Santoro 2000 0/75 1/75 0.1 % 0.33 [0.01, 8.20]
Woods 1992 90/1150 118/1150 4.0 % 0.74 [0.56, 0.99]
Subtotal (95% CI) 16320 16286 49.9 % 1.00 [0.93, 1.08]
Total events: 1503 (Treatment), 1502 (Control)
Heterogeneity: Chi² = 16.41, df = 7 (P = 0.02); I² =57%
Test for overall effect: Z = 0.05 (P = 0.96)
Wu 1992 5/125 12/102 0.5 % 0.31 [0.11, 0.92]
Zhu 2002 101/1691 134/1488 4.9 % 0.64 [0.49, 0.84]
Subtotal (95% CI) 2596 2385 8.0 % 0.55 [0.44, 0.69]
Total events: 139 (Treatment), 222 (Control)
Heterogeneity: Chi² = 14.04, df = 12 (P = 0.30); I² =15%
Test for overall effect: Z = 5.26 (P < 0.00001)
Total (95% CI) 36330 36142 100.0 % 0.99 [0.94, 1.04]
Total events: 2936 (Treatment), 2958 (Control)
Heterogeneity: Chi² = 57.77, df = 22 (P = 0.00005); I² =62%
Test for overall effect: Z = 0.48 (P = 0.63)
0.1 0.2 0.5 1 2 5 10
Favours treatment
Favours control

Knowledge synthesis



Do it right

Subgroup & Sensitivity Analysis

Subgroup Analysis – MA of a subgroup of eligible studies

[Investigating heterogeneous results and more specific questions relevant to particular clinical patient groups]

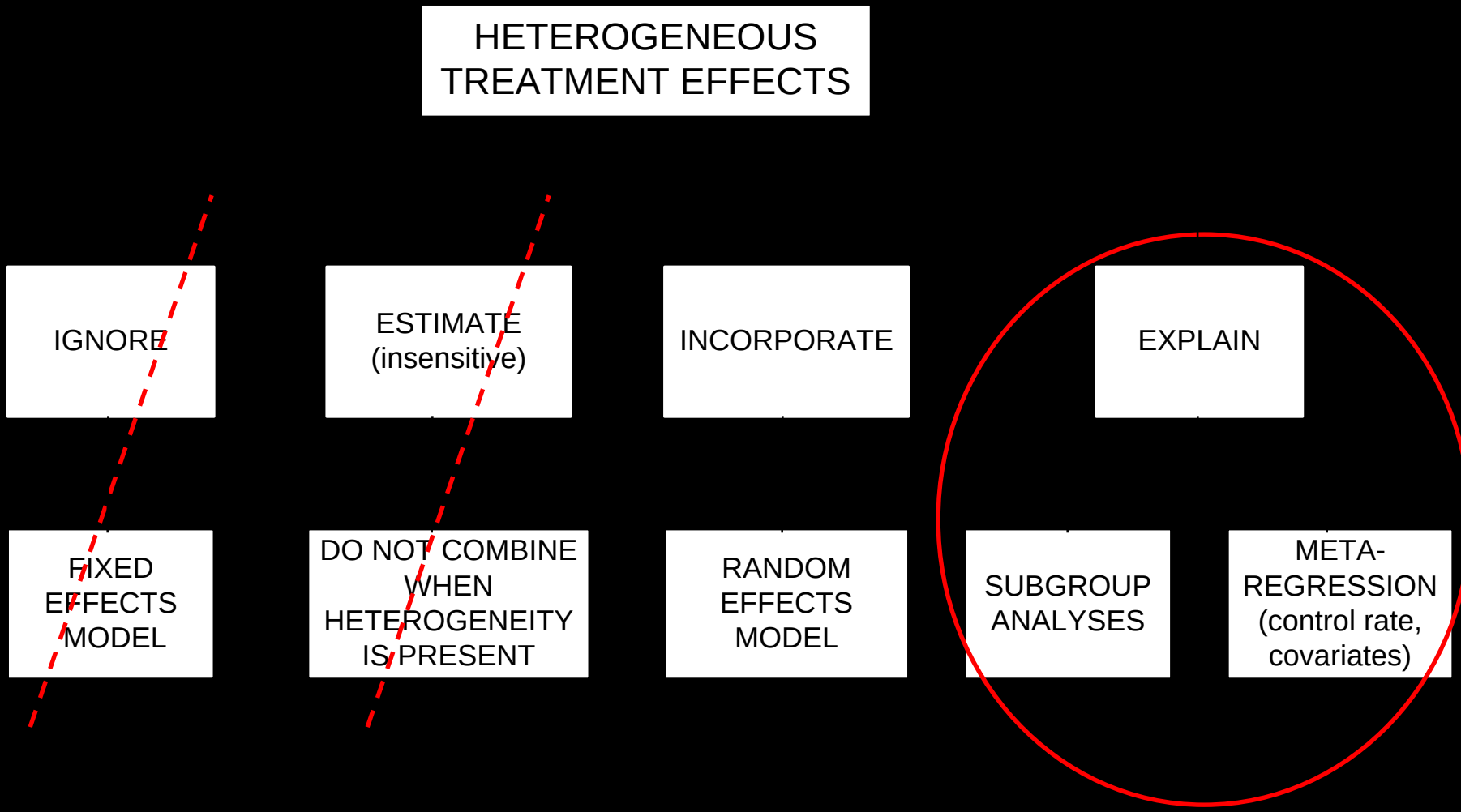
- age
- ethnicity

Sensitivity Analysis – add or delete questionable studies

[Testing how robust the results of the review are relative to key decisions and assumptions that were made in the process of conducting the review]

- eligibility
- treatment (integrity)

Subgroup analyses might be part of a sensitivity analysis and vice versa


HETEROGENEOUS TREATMENT EFFECTS
IGNORE
ESTIMATE (insensitive)
INCORPORATE
EXPLAIN
FIXED EFFECTS MODEL
DO NOT COMBINE WHEN HETEROGENEITY IS PRESENT
RANDOM EFFECTS MODEL
SUBGROUP ANALYSES
META-REGRESSION (control rate, covariates)